SCIENTIFIC ABSTRACT

Our long-term objective is to develop clinically effective and broadly applicable vaccine strategies for a wide range of cancer patients by inducing immunity against the protein subunit of human telomerase, telomerase reverse transcriptase (hTERT). Telomerase is an attractive candidate for a broadly expressed tumor rejection antigen since telomerase is silent in normal tissues but is reactivated and over expressed in the majority of human solid tumors. We have performed preclinical studies demonstrating that autologous DC transfected with TERT RNA are a remarkable effective strategy to stimulate TERT-specific CTL *in vitro* from the PBMC of cancer patients. Moreover, we have demonstrated that a modification of the LAMP template by inserting the lysosomal targeting signal LAMP may further enhance the efficacy of this approach by optimally stimulating CD8 and CD 4 T cell responses. Having established the conditions for optimal generation of hTERT specific CD8 and CD4 T cell responses in vitro we will now pursue with the conduct of a phase I clinical trial designed to evaluate the safety of administering hTERT RNA and LAMP-hTERT RNA transfected, cytokine matured DC to patients with metastatic prostate cancer. We hypothesize that administration of escalating doses of hTERT RNA transfected DC to patients with metastatic RCC is safe and will lead to detectable levels of TERT specific T cells in the peripheral blood of prostate cancer patients. Moreover, we propose to analyze the bioactivity of TERT RNA transfected DC by measuring the presence, magnitude and duration of hTERT specific CD8 and CD4 T cell responses from peripheral blood of study subjects prior enrolled in both treatment arms by (a) analyzing changes in the post treatment cytokine profiles of activated T cells as assessed by an automated ELISPOT assay; (b) measuring the frequency of hTERT epitope specific CTL by tetramer analysis, c) measuring the functional capability of the *in vivo* generated CTL to specifically recognize and lyse TERT expressing or tumor targets, and d) determine the presence of CD4 T cell responses by conventional proliferation assays or by novel, simplified whole blood assays using cytokine flow-cytometry. The proposed project will set the stage for scientifically valid phase II studies to assess the clinical efficacy of vaccinating renal cancer patients with hTERT RNA transfected DC and evaluate the utility of using hTERT as antigen to treat a wide range of cancers, which overexpress hTERT.